

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

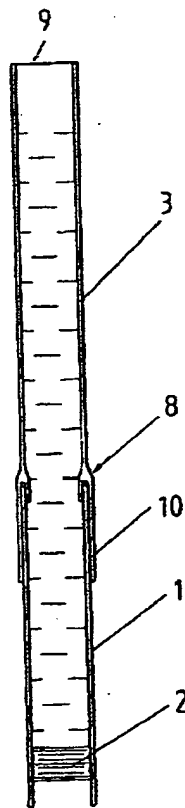
- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Problem Image Mailbox.**



- (72) VETTER, Helmut, DE
(72) OTTO, Thomas, DE
(71) ARZNEIMITTEL GMBH APOTHEKER VETTER & CO.
RAVENSBURG, DE
(51) Int.Cl.⁶ A61M 5/31
(30) 1997/11/19 (197 51 226.7-27) DE
(54) **PROCESSUS DE REMPLISSAGE D'UNE SERINGUE ET
DISPOSITIF POUR EXECUTER LE PROCESSUS**
(54) **PROCESS FOR FILLING A SYRINGE, TOGETHER WITH A
DEVICE FOR CARRYING OUT THE PROCESS**



(57) The procedure according to the invention for filling a syringe, and more particularly a syringe for medical purposes, with a substance, which once filled into the syringe undergoes a volume-reducing step in the process, and more particularly a lyophilization. To achieve this a dose dispenser which is open to the syringe barrel and which is sealed against it is first placed at the end of the syringe barrel which is to be filled. Next the substance is introduced into the dose dispenser as well as the syringe barrel and the substance filling the syringe barrel and the dose dispenser is submitted to the volume-reducing process. Then the dose dispenser is removed from the syringe barrel and the syringe barrel is sealed or else conveyed along to further steps in the process.

**PROCESS FOR FILLING A SYRINGE, TOGETHER
WITH A DEVICE FOR CARRYING OUT THE PROCESS**

Abstract

The procedure according to the invention for filling a syringe, and more
5 particularly a syringe for medical purposes, with a substance, which once filled into the
syringe undergoes a volume-reducing step in the process, and more particularly a
lyophilization. To achieve this a dose dispenser which is open to the syringe barrel
and which is sealed against it is first placed at the end of the syringe barrel which is to
be filled. Next the substance is introduced into the dose dispenser as well as the
10 syringe barrel and the substance filling the syringe barrel and the dose dispenser is
submitted to the volume-reducing process. Then the dose dispenser is removed from
the syringe barrel and the syringe barrel is sealed or else conveyed along to further
steps in the process.

- 1 -

PROCESS FOR FILLING A SYRINGE, TOGETHER WITH A DEVICE FOR CARRYING OUT THE PROCESS

Technical Field

The subject of the invention is a process for filling a syringe with a substance, wherein the substance is introduced into the syringe with an initial volume that is greater than the volume of the syringe, and the substance subsequently undergoes a
5 reduction in volume to a volume less than or equal to the volume of the syringe.

The invention further relates to a device for the performance of this process.

Background of the Invention

In the manufacture of syringes pre-filled with pharmaceutical substances, it is often necessary first to free the substances which are present in dissolved form from
10 their solvent, in order to obtain a sufficiently long shelf life for the substance. This is generally performed through freeze-drying (lyophilization). The product in freeze-dried condition frequently possesses a significantly higher stability and, consequently, longer shelf life. Such lyophilized pharmaceutical products are most generally introduced into what is known as a dual chamber syringe, in which one of the two
15 chambers is filled with a suitable solvent, which is added immediately before use, in order to dissolve the lyophilized product. Often the lyophilisate, after freeze-drying has been performed, takes up the same space as it did in dissolved form.

Among the products which are lyophilized and which must be reconstituted before application by means of a solvent, there are those which are administered to the
20 patient in their lyophilized form (as lyophilisate). It is desirable for subsequent use of such substances that they undergo a reduction in volume during the freeze-drying process, so that the user is able to apply them more selectively. However, after lyophilization has been performed, there usually remains a large superfluous volume that was required for filling the syringe with the product in its dissolved form.

25 This extra volume thus takes up space and it can also be an inconvenience to the user during application of the substance.

- 2 -

The invention solves this problem by proposing a process for filling a syringe as well as a device suitable for the performance thereof, which allows the use of a syringe size appropriate to the volumes of the lyophilized products, thus permitting the effective filling of the syringe, while at the same time the possibility remains for the
5 injection system to offer the maximum size of opening, that is, to present no narrowing in the head area (the end into which the cannula or needle is inserted).

This problem is solved in the process according to the invention by inserting against the end of the syringe barrel to be filled a dose dispenser that is open towards the syringe barrel and forms a seal with it. A substance in the dose dispenser can then
10 be introduced into the syringe barrel filling both the syringe barrel and the dose dispenser. Subsequently the volume of the substance is reduced whereupon the dose dispenser is detached from the syringe barrel and the syringe barrel closed or passed along to further steps in the process.

Summary of the Invention

15 In accordance with one aspect of the present invention there is provided a process for filling a syringe with a substance, comprising the steps of (A) fitting a dose dispenser onto an end of the syringe, such that the dose dispenser forms an extension of the syringe volume and is sealed to the syringe; (B) introducing a first volume of the substance in liquid form into the dose dispenser such that it flows into the syringe;
20 (C) reducing the volume of the substance to a second volume by evaporation; and (D) removing the dose dispenser from the syringe; wherein the first volume fills the syringe and at least partially fills the dose dispenser, and the second volume resides entirely within the syringe.

In accordance with another aspect of the present invention there is provided a
25 device for filling a syringe with a substance to be lyophilized, comprising a vessel which forms an extension of the syringe when sealably attached on an end of the syringe, and attaching means for sealably attaching the vessel on the end of the syringe.

- 3 -

Detailed Description of Preferred Embodiments

The advantage conferred by the invention consists substantially in that the effective volume of the syringe is momentarily increased by the dose dispenser. As lyophilization progresses, an increasingly smaller volume of the solvent of the substance is in the syringe barrel, so that at the end of the lyophilization process the dose dispenser can be removed and is then available for further use.

In the device according to the invention the problem is solved by a syringe, and more particularly a syringe for medical purposes, with a substance which when filled in the syringe undergoes a volume-reducing step in the process, and more particularly a lyophilization, and in which the syringe is formed by a syringe barrel and a stopper arranged therein, and on one of whose ends a needle attachment or cover piece is fitted, and on its other end a finger support or rest with plunger rod can be fitted, while a dose dispenser, which can be installed on one of the two ends of the syringe barrel by attachment means, is in this way open to the syringe barrel and sealed against it, and which when installed on the syringe barrel presents on its upper end an opening for filling with the substance.

In a preferred embodiment of the invention the dose dispenser attachment means is formed by a cylindrical sleeve which conformably grips the syringe barrel externally.

It is advantageous if the dose dispenser attachment means presents a collar projecting into the interior of the syringe barrel, and which for sealing is provided with a receiving groove on the sleeve surface presented to the wall of the syringe barrel. In this way it is more particularly ensured that the area of the interior sleeve surface between the seal and the face of the syringe barrel does not come into contact with the solvent or the lyophilisate, since when the syringe barrel is subsequently closed a sealing stopper is generally inserted in this area.

In a preferred embodiment, a seal is inserted in the annular groove formed between the cylindrical sleeve and the collar.

It is further provided according to an embodiment of the invention that the cylindrical sleeve projects axially beyond the collar.

- 4 -

It is preferred that the dose dispenser have the same cross-sectional shape and dimensions as the syringe barrel.

In the Drawings

- 5 Fig. 1: A syringe barrel with a dose dispenser attached filled with a solution to be lyophilized;
- Fig. 2: As in Fig. 1, however after lyophilization has been completed;
- Fig. 3: The syringe closed and fully sealed after completion of lyophilization and with the dose dispenser removed;
- Fig. 4: A representation of the detail identified as "X" in Fig. 3.

10 The device represented in the drawings serves to fill a syringe, and more particularly a syringe for medical purposes, with a substance, which, after it is filled into the syringe, is subjected to a volume-reducing step. An example of such a volume reducing step is lyophilization. In a process according to the invention an active substance contained in a liquid solvent is introduced into the syringe barrel and the
15 solvent is removed by lyophilization, so that the active substance itself is then present in freeze-dried form. In order to prevent that for a wide variety of reasons a large free volume remains in the syringe barrel 1 as a result of lyophilization, a dose dispenser 3 is provided, which can be superimposed upon one of the two ends of the syringe barrel 1. In the typical embodiment provision is made to emplace the dose dispenser 3 on
20 the end of the syringe barrel 1 in which the needle is inserted, while the other end is closed by a stopper 2.

 In this situation, the dose dispenser 3 is open towards the syringe barrel 1 and forms a seal with it. As emplaced on the syringe barrel 1 the dose dispenser 3 presents at its upper end a filler opening 9 for the substance.

25 More specifically, the attachment piece 8 of the dose dispenser 3 is formed from a cylindrical sleeve 1 which conformably grips the exterior of the syringe barrel 1. Moreover, the attachment piece 8 of the dose dispenser 3 is provided with a collar 11 projecting into the interior of the syringe barrel, and which is provided with a locking groove for a seal 4 on the sleeve surface presented to the wall of the syringe

- 5 -

barrel 1. This seal 4 can more clearly be distinguished in the enlarged representation as shown in Fig. 4. This seal 4, which when the dose dispenser is completely filled is located at a distance from the end of the syringe barrel 1, additionally ensures that the rim area adjoining the face of the syringe barrel 1 is kept free from solvent and lyophilisate and thus forms a suitably clean sealing surface for the subsequently inserted stopper 4 or the like.

As can be seen in Fig. 4, an additional seal 5 can also be inserted in the annular groove formed between the cylindrical sleeve 10 and the collar 11.

To give the dose dispenser 3 a particularly strong grasp on the syringe barrel 1, the cylindrical sleeve 10 projects axially over the collar 11. It is preferred that the dose dispenser 3 and the syringe barrel 1 have the same cross-sectional shape and dimensions. In the figures, the upper end of the dose dispenser 3 corresponds exactly in its shape to the upper end of the syringe barrel 1 itself, as a result of which when the dose dispenser 3 is in use no adjustments or modifications whatever of the filling device are required, except for an adjustment in height.

The steps of the process shown in detail in Figs. 1 to 3 proceed in such a way that the dose dispenser 3 is first located on syringe barrel 1. The dose dispenser and syringe are filled with a solution of the desired substance, so that the filling, which in Fig. 1 is indicated by horizontal dashes, extends almost to the upper edge of the dose dispenser 3.

The solution of the substance is lyophilized.

After lyophilization the dried substance, indicated in Fig. 2 by shorter horizontal dashes, is located exclusively in the syringe barrel 1, so that the dose dispenser 3 can be removed and the syringe barrel 1 can be closed by means of stopper 6 and a suitable cover piece 7, as shown in Fig. 3.

- 6 -

What is claimed:

1. A process for filling a syringe with a substance, comprising the steps of
(A) fitting a dose dispenser onto an end of the syringe, such that the dose
dispenser forms an extension of the syringe volume and is sealed to the syringe;
5 (B) introducing a first volume of the substance in liquid form into the dose
dispenser such that it flows into the syringe;
(C) reducing the volume of the substance to a second volume by
evaporation; and
(D) removing the dose dispenser from the syringe;
10 wherein the first volume fills the syringe and at least partially fills the dose
dispenser, and the second volume resides entirely within the syringe.
2. A process according to claim 1, wherein step (C) is carried out by
lyophilization.
3. A process according to claim 1 or 2, wherein the syringe is for medical
15 purposes.
4. A device for filling a syringe with a substance to be lyophilized,
comprising
a vessel which forms an extension of the syringe when sealably attached on an
end of the syringe, and attaching means for sealably attaching the vessel on the end of
20 the syringe.
5. A device according to claim 4, wherein the vessel is cylindrical in
shape, and has approximately the same cross-sectional shape as the syringe barrel.
6. A device according to claim 4 or 5, wherein the attachment means
comprises a cylindrical sleeve which, in use, sealably grips the exterior of the syringe
25 barrel.

- 7 -

7. A device according to claim 6, wherein the attachment means further comprises a cylindrical collar projecting into the interior of the syringe barrel, thereby, in use, forming a seal with the interior wall of the syringe barrel.

8. A device according to claim 7, wherein the cylindrical collar is provided with a groove for sealing means in the surface whereby, in use, the sealing means forms a seal with the interior wall of the syringe.

9. A device according to claim 7 or 8, comprising sealing means placed in an annular groove formed by the cylindrical sleeve and the cylindrical collar.

10. A device according to claim 7, 8 or 9, wherein the cylindrical sleeve projects axially beyond the cylindrical collar.

11. A process for filling a syringe, and more particularly a syringe for medical purposes, which when filled with a substance undergoes a lyophilization process, in which the filling at the end of the process presents a reduction in volume in comparison to its dissolved form, and characterized in that on the end of the syringe barrel to be filled is placed a dose dispenser open to the syringe barrel and sealed against it, so that the substance introduced into the dose dispenser and in the syringe barrel and the substance then filling the syringe barrel as well as the dose dispenser can then be subjected to a volume-reducing process step, and that finally the dose dispenser is removed from the syringe barrel and the syringe barrel closed or else conveyed along to further steps in the process.

12. A device for filling a syringe following to the process according to claim 11, and more particularly a syringe for medical purpose, with a substance which, when filled into the syringe undergoes a volume-reducing step in the process, and more particularly a lyophilization, in which the syringe consists of a syringe barrel and a stopper located inside it, and on whose one end can be located a needle attachment or cover piece and on whose other end can be located a finger supported with a plunger

- 8 -

actuating rod, characterized by a dose dispenser, which can be attached to one of the two ends of the syringe barrel with an attachment piece, and which is open to the syringe barrel and sealed against it, and which when fitted onto the syringe barrel presents a filler opening for the substance.

5 13. A device according to Claim 12, characterized in that the attachment piece of the dose dispenser has the form of a cylindrical sleeve, which conformably grips the exterior of the syringe barrel.

 14. A device according to Claim 12 or 13, characterized in that the attachment piece of the dose dispenser presents a collar projecting into the interior of
10 the syringe barrel, whose enclosing surface presented to the wall of the syringe barrel is provided with a receiving groove for a seal.

 15. A device according to Claim 14, characterized in that a seal is inserted in the annular groove formed between the cylindrical sleeve and the collar.

 16. A device according to Claim 14 or 15, characterized in that the
15 cylindrical sleeve projects axially beyond the collar.

 17. A device according to any one of Claims 12 to 16, characterized in that the dose dispenser has the same cross-sectional form and dimensions as the syringe barrel.

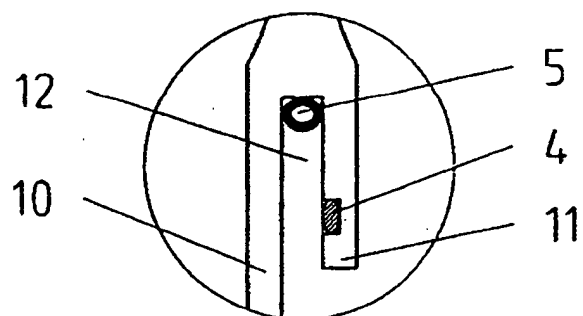


Fig. 4

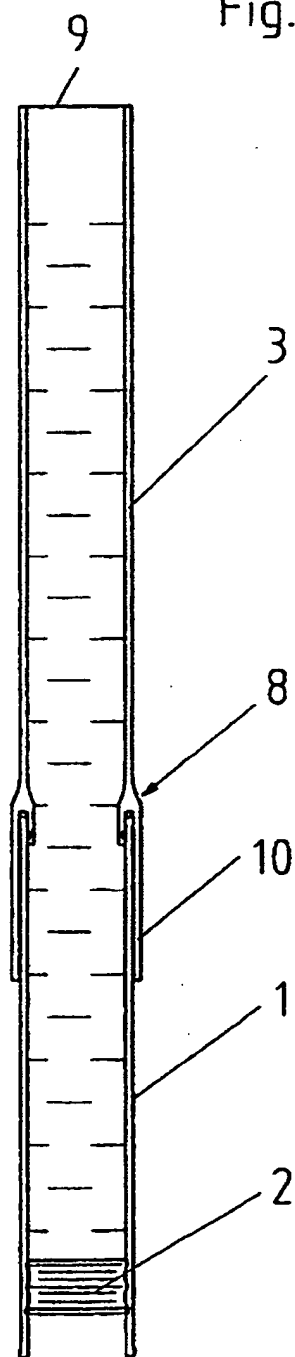


Fig. 1

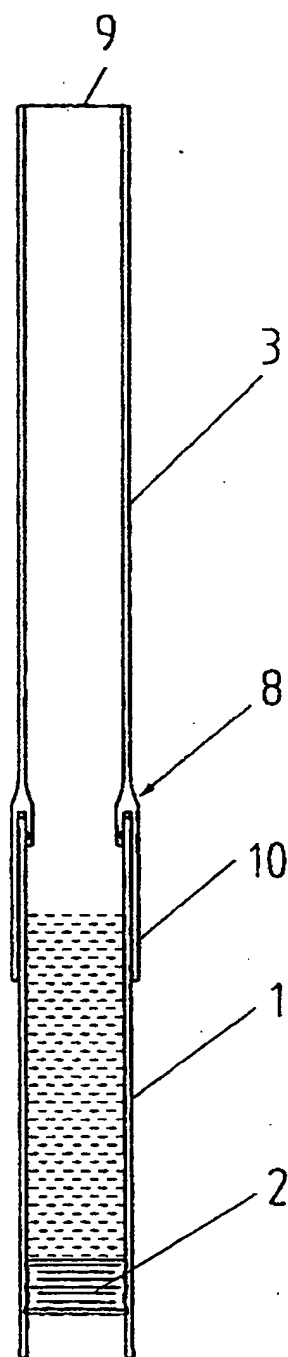


Fig. 2

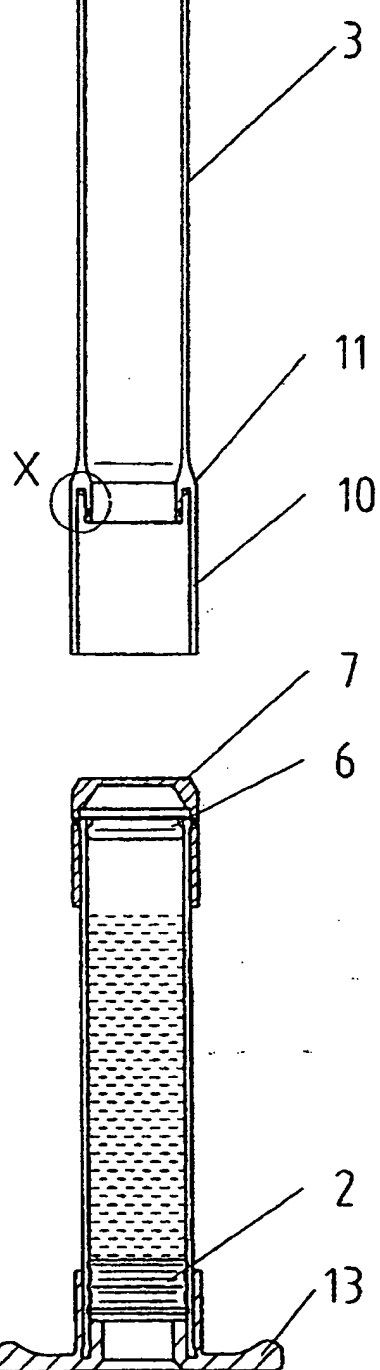


Fig. 3